

CLAIMS

We Claim:

- 1 1. A molecule of the structure **A – X – B**, wherein
2 **B** is a peptide portion of about 5 to about 20 basic amino acid
3 residues, which is suitable for cellular uptake,
4 **A** is a peptide portion of about 2 to about 20 acidic amino acid
5 residues, which when linked with portion **B** is effective to inhibit or prevent
6 cellular uptake of portion **B**, and
7 **X** is a linker of about 2 to about 100 atoms joining **A** with **B**, which
8 can be cleaved under physiological conditions.
- 1 2. The molecule of claim 1, wherein said peptide portion **A** comprises
2 about 5 to about 9 glutamates or aspartates.
- 1 3. The molecule of claim 2, wherein said peptide portion **A** comprises
2 about 5 to about 9 consecutive glutamates or aspartates.
- 1 4. The molecule of claim 1, wherein said peptide portion **B** comprises
2 about 9 to about 16 arginines.
- 1 5. The molecule of claim 4, wherein said peptide portion **B** comprises
2 about 9 to about 16 consecutive arginines.
- 1 6. The molecule of claim 1, wherein said peptide portion **A** comprises
2 D-amino acids.
- 1 7. The molecule of claim 1, wherein said peptide portion **B** comprises
2 D-amino acids.

1 8. The molecule of claim 1, wherein said peptide portion **A** consists of
2 D-amino acids.

1 9. The molecule of claim 1, wherein said peptide portion **B** consists of
2 D-amino acids.

1 10. The molecule of claim 1, wherein said peptide portions **A** and **B**
2 consists of D-amino acids.

1 11. A molecule for transporting a cargo moiety across a cell membrane
2 of the structure **A – X – B – C**, wherein

3 **C** is a portion comprising a cargo moiety,

4 **B** is a peptide portion of about 5 to about 20 basic amino acid
5 residues, which is suitable for cellular uptake, is covalently linked to portion **C**,
6 and is effective to enhance transport of cargo portion **C** across a cell membrane,

7 **A** is a peptide portion of about 2 to about 20 acidic amino acid
8 residues, which when linked with portion **B** is effective to inhibit or prevent
9 cellular uptake of **B – C** , and

10 **X** is a cleavable linker of about 2 to about 100 atoms joining **A** with
11 **B – C**, which can be cleaved under physiological conditions.

1 12. The molecule of claim 11, wherein said peptide portion **A** comprises
2 amino acids selected from the group of acidic amino acids consisting of glutamate
3 and aspartate.

1 13. The molecule of claim 11, wherein said peptide portion **B** comprises
2 amino acids selected from the group of basic amino acids consisting of arginine
3 and histidine.

1 14. The molecule of claim 11, wherein said cargo portion **C** is selected
2 from the group of cargo moieties consisting of a fluorescent moiety, a
3 fluorescence-quenching moiety, a radioactive moiety, a radiopaque moiety, a
4 paramagnetic moiety, a nanoparticle, a vesicle, a molecular beacon, a marker, a
5 marker enzyme, a contrast agent, a chemotherapeutic agent, and a radiation-
6 sensitizer.

1 15. The molecule of claim 14, wherein the cargo portion **C** comprises a
2 contrast agent for diagnostic imaging.

1 16. The molecule of claim 14, wherein the cargo portion **C** comprises a
2 radiation sensitizer for radiation therapy.

1 17. The molecule of claim 11, wherein said peptide portion **A** comprises
2 about 5 to about 9 glutamates or aspartates.

1 18. The molecule of claim 17, wherein said peptide portion **A** comprises
2 about 5 to about 9 consecutive glutamates or aspartates.

1 19. The molecule of claim 11, wherein said portion peptide **B** comprises
2 between about 9 to about 16 arginines.

1 20. The molecule of claim 19, wherein said peptide portion **B** comprises
2 between about 9 to about 16 consecutive arginines.

1 21. The molecule of claim 11, wherein said peptide portion **A** comprises
2 D-amino acids.

1 22. The molecule of claim 11, wherein said peptide portion **B** comprises
2 D-amino acids.

1 23. The molecule of claim 11, wherein said peptide portion **A** consists of
2 D-amino acids.

1 24. The molecule of claim 11, wherein said peptide portion **B** consists of
2 D-amino acids.

1 25. The molecule of claim 11, wherein said peptide portions **A** and **B**
2 consist of D-amino acids.

1 26. The molecule of claim 25, wherein said peptide portion **B** consists of
2 D-arginine amino acids.

1 27. The molecule of claim 11, wherein said peptide portion **A** is located
2 at a terminus of a polypeptide chain comprising **B - C**.

1 28. The molecule of claim 11, wherein said peptide portion **A** is located
2 at the amino terminus of a polypeptide chain comprising **B - C**.

1 29. The molecule of claim 11, wherein said peptide portion **A** is linked
2 near to or at the amino terminus of a polypeptide chain comprising **B - C**.

1 30. The molecule of claim 11, wherein said peptide portion **A** is linked
2 near to or at the carboxy terminus of a polypeptide chain comprising **B - C**.

1 31. The molecule of claim 11, wherein **B - C** comprises a polypeptide
2 chain having ends consisting of a **B-side** terminus and a **C-side** terminus, and
3 wherein cleavable linker **X** is disposed near or at said **B-side** terminus.

1 32. The molecule of claim 11, wherein **B - C** comprises a polypeptide
2 chain having ends consisting of a **B-side** terminus and a **C-side** terminus, and
3 wherein cleavable linker **X** is disposed near or at said **C-side** terminus.

1 33. The molecule of claim 11, wherein cleavable linker **X** is a flexible
2 linker.

1 34. The molecule of claim 11, wherein cleavable linker X is a flexible
2 linker about 6 to about 30 atoms in length.

1 35. The molecule of claim 11, wherein cleavable linker X is cleavable in
2 an acidic environment.

1 36. The molecule of claim 11, wherein cleavable linker X is comprises a
2 peptide linkage.

1 37. The molecule of claim 11, wherein cleavable linker X comprises
2 aminocaproic acid.

1 38. The molecule of claim 11, wherein cleavable linker X is configured
2 for cleavage exterior to a cell.

1 39. The molecule of claim 11, wherein cleavable linker X is configured
2 for cleavage by an enzyme.

1 40. The molecule of claim 38, wherein said enzyme is a matrix
2 metalloprotease.

1 41. The molecule of claim 35 wherein cleavable linker X comprises the
2 amino acid sequence PLGLAG (SEQ ID NO:1).

1 42. The molecule of claim 35 wherein cleavable linker X comprises the
2 amino acid sequence EDDDDKA (SEQ ID NO:2).

1 43. The molecule of claim 34 wherein cleavable linker X comprises a S
2 - S linkage.

1 44. The molecule of claim 34, wherein cleavable linker X comprises a
2 transition metal complex, wherein said transition metal complex linker is cleaved
3 when the metal is reduced.

1 45. The molecule of claim 11, comprising a plurality of cleavable linkers
2 **X** linking a portion **A** to a structure **B - C**.

1 46. A pharmaceutical composition comprising:

2 A molecule of the structure **A - X - B**, wherein

3 **B** is a peptide portion of about 5 to about 20 basic amino acid
4 residues, which is suitable for cellular uptake,

5 **A** is a peptide portion of about 2 to about 20 acidic amino acid
6 residues, which when linked with portion **B** is effective to inhibit or prevent
7 cellular uptake of portion **B**, and

8 **X** is a cleavable linker of about 3 to about 30 atoms joining **A** with
9 **B**, which can be cleaved under physiological conditions; and

10 a pharmaceutically acceptable carrier.

1 47. The pharmaceutical composition of claim 46, wherein

2 said cleavable linker **X** is of between about 6 to about 30 atoms in length,
3 said portion **A** has between about 5 to about 9 acidic amino acid residues, and said
4 portion **B** has between about 9 to about 16 basic amino acid residues.

1 48. The pharmaceutical composition of claim 46 or 47, further
2 comprising a portion **C** covalently attached to said portion **B** and comprising a
3 cargo moiety.

1 49. A method of modulating cellular uptake of a peptide **B** of about 5 to
2 about 20 basic amino acid residues, which is suitable for cellular uptake,
3 comprising:

4 linking said peptide **B** to a peptide **A** of about 2 to about 20 acidic amino
5 acid residues with a cleavable linker **X** of about 3 to about 30 atoms, which can be
6 cleaved under physiological conditions and

7 cleaving said cleavable linker **X** effective to separate peptide **B** from
8 molecule **A**.

1 50. A method of modulating cellular uptake of a cargo moiety **C**,
2 comprising:

3 covalently attaching a cargo moiety **C** to a peptide **B** of about 5 to about 20
4 basic amino acid residues to form a molecule **B - C**;

5 linking said molecule **B - C** to a peptide **A** of about 2 to about 20 acidic
6 amino acid residues with a cleavable linker **X** of about 3 to about 30 atoms, and

7 cleaving said cleavable linker **X** effective to separate **B - C** from said
8 peptide **A**.

1 51. A nucleic acid encoding a molecule of the structure **A - X - B**,
2 wherein

3 **B** is a peptide of about 5 to about 20 basic amino acid residues,
4 which is suitable for cellular uptake,

5 **A** is a peptide of about 2 to about 20 acidic amino acid residues,
6 which when linked with peptide **B** is effective to inhibit or prevent cellular uptake
7 of peptide **B**, and

8 **X** is a cleavable linker portion of between 1 and 10 amino acid
9 residues joining **A** with **B**, which can be cleaved under physiological conditions.

1 52. A nucleic acid encoding a molecule of the structure **A – X – B – C**,
2 wherein

3 **C** is a peptide cargo moiety,

4 **B** is a peptide of about 5 to about 20 basic amino acid residues,
5 which is suitable for cellular uptake,

6 **A** is a peptide of about 2 to about 20 acidic amino acid residues,
7 which when linked with peptide **B** is effective to inhibit or prevent cellular uptake
8 of peptide **B - C**, and

9 **X** is a cleavable linker portion of between 1 and 10 amino acid
10 residues joining **A** with **B – C** which can be cleaved under physiological
11 conditions.

12 53. A molecule for transporting a fluorescent cargo moiety across a cell
13 membrane of the structure **Q - A – X – B - C**, wherein

14 **C** is a portion comprising a fluorescent cargo moiety,

15 **B** is a peptide portion of about 5 to about 20 basic amino acid
16 residues, which is suitable for cellular uptake, is covalently linked to portion **C**,
17 and is effective to enhance transport of cargo portion **C** across a cell membrane,

18 **Q** is a quencher moiety attached to **A** and effective to quench
19 fluorescence from fluorescent cargo **C**;

20 **A** is a peptide portion of about 2 to about 20 acidic amino acid
21 residues, which when linked with portion **B** is effective to inhibit or prevent
22 cellular uptake of **B - C** , and

23 **X** is a cleavable linker of about 2 to about 100 atoms joining **A** with
24 **B – C**, which can be cleaved under physiological conditions.

25 54. The molecule of claim 39, wherein said enzyme is a protease.

26 55. The molecule of claim 54, wherein, upon cleavage of said linker **X**,
27 said linker **X** has a C-terminus and said portion **B** has an N terminus, whereby
28 upon cleavage of linker **X** said N terminus of portion **B** may provide an additional
29 positive charge to portion **B** under physiological conditions.

30 56. The molecule of claim 11, comprising a single cargo portion **C**
31 linked to a plurality of portions **B**, each of portions **B** being linked to a cleavable
32 linker portion **X** linked to an acidic portion **A**.